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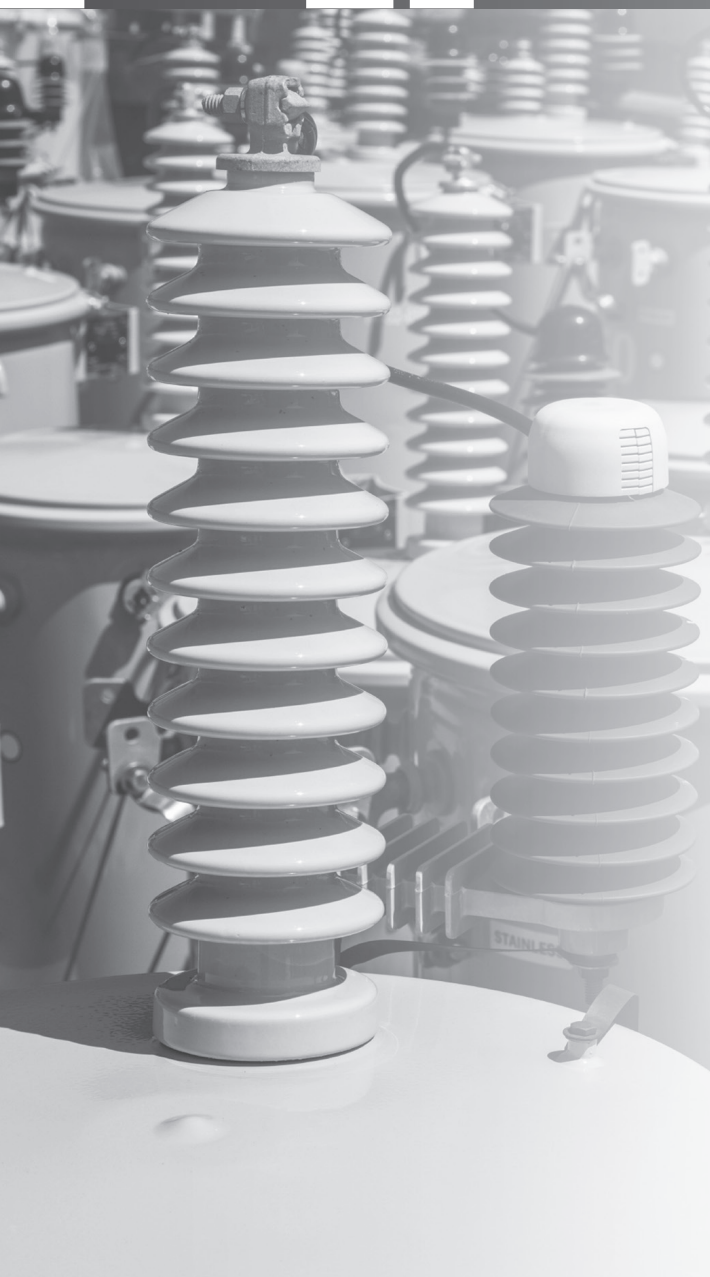

POLYCHLORINATED BIPHENYLS AND POLYBROMINATED BIPHENYLS

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5. SUMMARY OF DATA REPORTED

5.1 Exposure data

Polychlorinated biphenyls (PCBs) are a class of aromatic chemical compounds in which some or all hydrogen atoms attached to the biphenyl nucleus are substituted by one to ten chlorine atoms. There are 209 congeners, which are arranged according to current nomenclature from 1 to 209 by increasing number of chlorines. Although physical and chemical properties vary widely across the class, PCBs generally have low solubility in water, high lipophilicity, and low vapour pressure; they are chemically stable and generally persist in the environment and in the human body.

PCBs are not known to occur naturally and have been produced commercially by a limited number of companies since 1929. Production peaked between the 1950s and the 1970s, and was banned in most countries by the 1980s; however, manufacturing in the Democratic People's Republic of Korea continued at least until 2006.

Commercial PCB products were manufactured to yield a given degree of chlorination to fulfil technical requirements. Products sold under different trade names (e.g. Aroclor, Clophen, Kanechlor) may be of similar composition with regard to the chlorine content. However, individual congeners have generally not been quantified in these products. A subset of PCBs are referred to as "dioxin-like PCBs," and have been assigned toxicity equivalency factors (TEFs) relative to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD).

Laboratory analyses of PCBs have improved in selectivity and sensitivity through the development of advanced instrumentation and analytical strategies allowing the identification and quantification of individual congeners within commercial products. State-of-the-art analytical methods enable detection of PCBs in virtually all types of sample; however, comparability with older methods is limited. Dioxin-like PCBs often occur in lower concentrations than other PCBs and are analysed together with polychlorinated dibenzodioxins and polychlorinated dibenzofurans. Apart from instrumental analysis, analyses based on biological response have been applied as screening tools.

Based on their physical and chemical properties, such as non-flammability, chemical stability, high boiling point, and high dielectric constant, products containing PCBs were widely used in several industrial, commercial, and military open and closed applications. The most important closed applications were as dielectric fluids in capacitors and transformers, and as hydraulic fluid and heat-transfer medium. Although these applications are considered as "closed," PCBs can still be released into the environment due to leakage. The most important open applications were as constituents of permanent elastic sealants, in polymers, and as flame-retardant coatings. To a lesser extent, PCBs were also used in inks, adhesives, dyes for carbonless duplicating paper, conveyor belts, and other rubber products, small ballasts for fluorescent lights, cutting

and lubricating oils, and metal coatings. In all open applications, PCBs can be released from the product into the environment via volatilization or erosion.

Once released into the environment, PCBs can be transported via environmental media and migratory species far from the site of production and use. PCBs are ubiquitous in the environment and are found in biota, air, soil, sediment, and water worldwide, including in polar regions and deep oceans. PCB concentrations vary by several orders of magnitude. Furthermore, congener patterns differ to varying degrees in air, water, sediments and soils as a consequence of transport, and transformation processes such as dechlorination. In the environment, PCBs volatilize easily, or are ingested by fish and other animals and transferred to the food chain, where their concentration may increase.

The general population is exposed primarily through ingestion of contaminated food. Food can become contaminated with PCBs by: (i) uptake from the environment by fish, birds, livestock; (ii) contamination of the foodstuffs through usual practice or industrial processing; and (iii) accidental contamination. In contrast to vegetables and crops, fatty foods typically contain high concentrations of PCBs. Most foodstuffs will have a shift in the congener profile in favour of less volatile, more highly chlorinated congeners.

Six congeners (PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, PCB-180) are found at high concentrations in the environment, food, and in human tissue. These congeners are often used to monitor exposure in epidemiological studies and are referred to as "indicator PCBs."

There have been two major episodes of human food contamination; both of which occurred in Asia; these episodes are commonly referred to as "Yusho" and "Yucheng." These populations were exposed through accidental contamination of cooking oil with either Kanechlor 400 or Kanechlor 500. Exposed people had blood PCB concentrations that were 100 to 1000 times higher than in the non-exposed population. Other accidental releases have occurred in the last few decades.

Indoor air can also contribute to human exposure to PCBs, owing to the use of PCBs in construction material. Exposure can occur in the workplace or at home; importantly, children may be exposed in schools and nurseries where PCB-containing materials have been used. Inhalation of PCBs results in a higher relative exposure to the more volatile, less chlorinated congeners.

Workers may be exposed during manufacturing, repair, use, and disposal of products or equipment containing PCBs. Earlier exposures to PCBs were higher and occurred during PCB manufacture, and filling of PCB-containing transformers and capacitors (up to 11 000 μg/m^3) and during the repair of transformers (up to 60 μg/m^3). More recent exposures may occur during abatement in construction (up to 120 μg/m^3), waste incineration, and recycling of electronic equipment and – to a lesser extent – working in PCB-contaminated buildings (up to 10 μg/m^3). It has been reported that workers in small-scale welding facilities in less developed countries may not use personal protective equipment when extracting PCB-contaminated coolant oil from discarded transformers, and are therefore likely to receive a considerable degree of exposure.

Historically, workers were exposed through inhalation and dermal contact, while occupational exposure to PCBs is nowadays primarily through dermal contact. In the past, workers were exposed during PCB manufacture and use to congener patterns that were similar to those of the products they handled, while today's workers are exposed to congener profiles that are different from those of the commercial mixtures. Occupational exposures to PCBs before the banning of PCB manufacture in the 1980s were much higher than those encountered today from

other sources. Since then, levels of occupational exposure to PCBs have been greatly reduced and now approach levels of environmental exposure.

5.2 Human carcinogenicity data

The association between exposure to PCBs and risk of cancer in humans has been evaluated in a large number of epidemiological studies in several occupational groups, in populations with elevated exposure to PCBs as a result of environmental incidents, and in the general population. Studies have been conducted in several countries, primarily in North America, Europe, and Asia, and have used cohort, nested case–control, and case–control designs.

The Working Group considered more than 70 separate studies with informative data regarding several cancer sites. The most important evidence regarding carcinogenicity came from studies of workers in industries where PCBs were used, and from population-based case–control studies. Occupational studies assessed exposure to PCB mixtures through job-exposure matrices and historical measurements, but most did not report data on non-occupational risk factors, which are important for some cancer sites. In case–control studies, analyses included adjustments for a larger range of risk factors and most used measurements of PCB concentrations (typically for specific congeners or groups of congeners) in blood or adipose tissue as indicators of exposure. The Working Group did not consider any exposure-assessment approach to be superior, each providing contrasting but useful information.

5.2.1 Malignant melanoma

Information on the association between risk of melanoma and exposure to PCBs was available primarily from cohort studies of capacitor- and transformer-manufacturing workers (four studies) and electric power and equipment workers (three studies) in North America and Europe. Excess risks of melanoma were reported in all studies except one. The only study reporting null results combined data from two plants in the USA: risk was significantly increased in the plant with predominantly white workers, but not in the second, where a large proportion of workers of African heritage were employed. Exposure–response relationships were evaluated in three studies and a statistically significant linear exposure–response trend was observed with a 20-year lag in the largest study, which included workers at five electric power companies.

Further evidence came from a high-quality case–control study of skin melanoma in Canada, which reported measurement of plasma concentrations of PCBs. This was the only case–control study in which the association between PCBs and melanoma was evaluated in the general population; the study used biological measurements of exposure and accounted for potential confounding factors. Trends were evaluated for dioxin-like PCBs, non-dioxin-like PCBs, and eight highly chlorinated individual congeners: all trends were positive and statistically significant. Additional support came from a multicentre European case–control study of uveal melanoma that assessed occupational exposure to oils containing PCBs and found positive associations.

The association between malignant melanoma and exposure to PCBs was consistently observed across studies of occupational exposure in different industries in several countries, in the general population, and with both cohort and case–control designs. These findings were unlikely to be a result of chance, since statistically significant associations were observed in large studies. Exposure–response relationships were also observed in several studies using different methodologies among exposed workers and in the general population. Confounding or other bias is unlikely to explain these results: there are few known risk factors for malignant melanoma other than sunlight, which was controlled for in

the case–control studies and in the only large study of occupational exposure that included outdoor workers for whom occupational exposure to sunlight could be significant. Exposure to sunlight is unlikely to confound associations in studies of indoor workers, since there is no reason to believe that exposure to sunlight during leisure time is associated with occupational exposure to PCBs.

5.2.2 Non-Hodgkin lymphoma

Data on the association of NHL and exposure to PCBs are available from studies of five independent occupational cohorts of capacitor manufacturing workers (three in the USA, one each in Italy and Sweden) and two cohorts of transformer manufacturing and repair workers (one in the USA, one in Canada). Four of these studies included specific assessments of the level of PCB exposure (three in the USA, one in Sweden). Statistically significant increases in mortality from NHL were observed in a cohort of capacitor manufacturing workers in Italy and among retired workers at a transformer manufacturing plant in the USA. Non-statistically significant increased risk of NHL was observed in the other capacitor and transformer manufacturing cohorts. However, a separate analysis of one of these latter cohorts by different investigators reported no excess of NHL. None of the four studies that assessed the level of PCB exposure found clear evidence of an exposure–response relationship The number of deaths from non-Hodgkin lymphoma was above that expected among men (deaths, $n = 4$) in a mortality follow-up study of a population in Taiwan, China, as a result of a mass poisoning episode with cooking oil contaminated with PCBs (Yucheng). However, no data on non-Hodgkin lymphoma were reported after a similar episode in Japan (Yusho), with a different exposure profile.

Nested case–control studies were conducted among subsamples of large population cohorts, and presented the advantage of having collected blood at recruitment, and having subsequently identified incident cases. Statistically significant trends in risk were associated with the sum of PCB congeners in three of the five studies considered; and were positive with specific congeners in several studies.

Four out of six good-quality case–control studies provided indications of a positive trend in risk of non-Hodgkin lymphoma with increasing plasma concentrations of the sum of PCBs. The results of a European case–control study of non-Hodgkin lymphoma were null overall, although heterogeneity was observed across the participating centres. A positive interaction was reported with markers of infection with Epstein-Barr virus (EBV), or with polymorphisms in genes encoding inflammatory cytokines, or an ancestral haplotype for human leukocyte antigen (HLA). Regarding non-Hodgkin lymphoma subtypes, follicular lymphoma, but not diffuse large B-cell lymphoma, was positively associated with exposure to PCBs in three studies.

In summary, the balance of evidence, taking into account study size and quality, suggested increased risk of non-Hodgkin lymphoma in relation to PCB exposure, and this is biologically plausible. However, since heterogeneous results were observed in high-quality studies, the Working Group could not exclude chance as a potential explanation for the associations observed. It is noteworthy that bias and confounding were excluded.

5.2.3 Cancer of the breast

Many studies investigated the risk of cancer of the breast in relation to exposure to PCBs, with the rationale that such an association is biologically plausible. The evidence that weighed most strongly in this evaluation came from 12 well designed and implemented case–control studies in the USA, Canada, and Japan that assessed risk in relation to concentrations of PCBs measured

in serum and/or adipose tissue. These studies each included between 175 and 750 cases of cancer of the breast, the controls being comparable women without cancer of the breast, and results were adjusted for relevant confounders. In one large study in the USA, no excess risk was seen, while in the other large study in the USA, increased risk of cancer of the breast in relation to PCBs was seen among African-American women, and among parous never-lactating white and African-American women combined. Of the 10 moderately sized studies, increased risks were seen in six studies in relation to PCBs, with some exposure–response relationships. In some of these studies, risk was also evaluated by subgroup, and increased risks were seen for women who were parous and had never lactated, for pre- and postmenopausal women, by various tumour characteristics, and by *CYP1A1* variants. Statistically significant increases in risk ranged from 1.1- to 4.3-fold. Three additional moderately sized studies from the USA reported no excess risk, while an inverse risk was seen in one study from Japan. Two additional case–control studies assessed PCBs through estimates of occupational or dietary exposure, and although the results suggested some increase in risk, these studies were not weighted strongly. In addition, most of the 10 smaller case–control studies reported some increased risks in relation to PCBs, although they were not weighted strongly in this evaluation due to the imprecise risk estimates.

While a few cohort studies of occupational exposure suggested an increased risk of cancer of the breast, PCB exposure was usually not assessed quantitatively in relation to risk, and important potential confounders were not taken into account. Within a case–control study nested among female capacitor workers, increased risk of cancer of the breast was seen for "non-white" (otherwise unspecified) women, taking into account non-occupational confounders. Other nested case–control studies (six from the USA, two from Denmark, and one from Norway) had a small or moderate number of cases and assessed PCBs in serum or adipose tissue with controls for confounders. The findings suggested some increased risks associated with some of the PCBs analysed, but the studies had limited power to assess associations.

On the balance of evidence, when taking into account study size, quality, and magnitude of risk, an increased risk of cancer of the breast was seen in relation to PCBs, with higher risks among some subgroups, and these associations are biologically plausible. Bias and confounding are unlikely to explain these results. However, as the results across high-quality studies were heterogeneous, the Working Group could not exclude chance as a possible explanation for positive associations.

5.2.4 Other cancer sites

Several other cancer sites were considered in one or more cohort or case–control studies. There were positive findings for cancer of the prostate and brain in several studies, but null findings in others. Other cancers with sporadic positive findings were those of the liver and biliary tract, extrahepatic biliary tract, lung and respiratory tract, thyroid, stomach, pancreas, colon and rectum, urothelial organs, uterus and ovary combined, as well as childhood acute lymphatic leukaemia, and multiple myeloma.

5.3 Animal carcinogenicity data

PCBs (individual congeners, binary mixtures, and commercial mixtures) were evaluated in rats and mice in studies of various design, and ranging in duration from several months up to 2 years. These included 2-year studies of carcinogenicity, studies involving transplacental/perinatal and postnatal exposure, initiation–promotion studies examining the promoting activity, and other co-carcinogenicity studies, using tumours as an end-point.

For the 2-year bioassays, the route of administration was oral, by gavage or feeding. In studies of initiation–promotion, co-carcinogenicity, and transplacental/perinatal exposure, PCBs were also administered intraperitoneally, subcutaneously, or by skin application. There were no studies of exposure by inhalation.

5.3.1 PCB congeners

PCB-126 was tested for carcinogenicity in one study in female rats treated by gavage. PCB-126 caused significant increases in the incidences of benign and malignant tumours of the liver (hepatocellular adenoma, hepatocholangioma, and cholangiocarcinoma), lung (cystic keratinizing epithelioma), and oral mucosa (gingival squamous cell carcinoma). In two studies of transplacental/perinatal exposure in female rats treated by gavage, PCB-126 had an inhibitory effect on the development of tumours of the mammary gland induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) in the offspring.

PCB-153 was tested for carcinogenicity in one study in female rats treated by gavage, one 4-month study of perinatal exposure in mice (including an initiation–promotion experiment), and one initiation–promotion study in mice. In the study of carcinogenicity, PCB-153 did not cause significant increases in the incidence of tumours in rats, but two rare cholangiomas were observed. PCB-153 promoted hepatocellular carcinomas induced by *N*-nitrosodiethylamine (NDEA) in mice. PCB-153 did not induce or promote bronchioloalveolar tumours in mice. PCB-153 was also evaluated as part of a binary mixture in a study examining the effect of increasing the dose of PCB-153 on the carcinogenicity of PCB-126 (see below); increasing the dose of PCB-153 increased the incidences of hepatocellular adenoma and cholangiocarcinoma when coadministered with PCB-126.

PCB-118 was tested for carcinogenicity in one study in female rats treated by gavage. PCB-118 caused significant increases in the incidences of benign and malignant tumours of the liver (hepatocellular adenoma, hepatocholangioma, and cholangiocarcinoma), benign tumours of the lung (cystic keratinizing epithelioma), and carcinoma of the uterus.

A binary mixture of PCB-126 and PCB-153 was tested for carcinogenicity in one study in female rats treated by gavage. The mixture of PCB-126 and PCB-153 caused significant increases in the incidences of hepatocellular adenoma, hepatocholangioma and cholangiocarcinoma, cystic keratinizing epithelioma of the lung, and squamous cell carcinoma of the oral mucosa. As stated above, increasing the proportion of PCB-153 to PCB-126 caused significant increases in the incidences of hepatocellular adenoma and cholangiocarcinoma in one study.

A binary mixture of PCB-118 and PCB-126 was tested for carcinogenicity in one study in female rats treated by gavage. The mixture caused significant increases in the incidences of hepatocellular adenoma, cholangiocarcinoma, and cystic keratinizing epithelioma of the lung.

When given to mice for 4 months, from the perinatal period to adulthood, PCB-138 was not carcinogenic, but did show evidence of a promoting effect based on a significant increase in the multiplicity of bronchioloalveolar adenomas induced by *N*-nitrosodimethylamine (NDMA).

A mixture of PCB-138 and PCB-153 was administered to mice for 4 months, from the perinatal period to adulthood. The mixture was not carcinogenic, and did not promote bronchioloalveolar tumours.

A mixture of non-*ortho*, mono-*ortho*, and di-*ortho* substituted PCB congeners, *p,p′*-dichlorodiphenyltrichloroethane (DDT) and *p,p′*-dichlorodiphenyldichloroethene (DDE) was tested for carcinogenicity in one study of perinatal exposure in rats treated by gavage. The mixture was not carcinogenic.

The hydroxylated mono-*ortho*-PCBs 2′,4′,6′-trichloro-4-biphenylol (4′-OH-PCB-30) and 2′,3′,4′,5′-tetrachloro-4-biphenylol

(OH-PCB-61), alone or as a binary mixture, were tested for carcinogenicity in one study of perinatal exposure in female mice treated by subcutaneous injection. Both the individual congeners and the binary mixture caused a significant increase in the total incidence of malignant tumours of the cervicovaginal tract (squamous cell carcinomas and adenosquamous carcinomas).

A mixture of the three non-*ortho* congeners PCB-77, PCB-126, and PCB-169, six polychlorinated dibenzodioxins, and seven polychlorinated dibenzofurans was tested for carcinogenicity in one study of perinatal exposure in female rats treated by gavage. The mixture caused a significant increase in the incidence of benign lesions of the mammary gland (hyperplasia, adenoma, and fibroadenoma).

A mixture of PCB-126, TCDD, and 2,3,4,7,8-pentachlorodibenzofuran was tested for carcinogenicity in one long-term study in female rats treated by gavage. The mixture caused a significant increase in the incidence of benign and malignant tumours of the liver (hepatocellular adenoma and cholangiocarcinoma) and benign tumours of the lung (cystic keratinizing epithelioma).

5.3.2 Aroclor

In a feeding study of carcinogenicity in male and female rats, Aroclor 1016 caused significant increases in the incidence of hepatocellular adenoma, and of hepatocellular adenoma or carcinoma (combined) in female rats.

In a feeding study of carcinogenicity in male and female rats, Aroclor 1242 caused significant increases in the incidence of hepatocellular adenoma in female rats, and of thyroid follicular cell adenoma, and thyroid follicular cell adenoma or carcinoma (combined) in males.

Aroclor 1254 was tested for carcinogenicity in two feeding studies in male and female rats, one feeding study in male mice, three studies of transplacental/perinatal exposure in mice, two studies examining promoting activity in male rats, five studies examining promoting activity in mice, and three co-carcinogenesis studies in mice. In rats, oral administration of Aroclor 1254 caused significant increases in the incidence of hepatocellular adenoma or carcinoma (combined) in males in the first study, and of hepatocellular adenoma and hepatocellular carcinoma in females, and of thyroid follicular cell adenoma, and follicular cell adenoma or carcinoma (combined) in males in the second study. In mice, oral administration of Aroclor 1254 caused significant increases in the incidence of "hepatomas" of the liver. In the studies of transplacental/perinatal exposure, Aroclor 1254 was not carcinogenic in mice, but promoted NDMA-induced bronchioloalveolar adenomas in two studies, and coalescing liver tumours in one study. In rats, Aroclor 1254 promoted NDEA-induced hepatocellular carcinomas in one study. In mice, Aroclor 1254 promoted NDEA-induced hepatocellular adenomas in one study, and NDEA-induced hepatocellular carcinomas, hepatoblastomas, and cholangiocellular tumours in another study. In a third study, Aroclor 1254 promoted lung tumours induced by NDMA and by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

Aroclor 1260 was tested for carcinogenicity in one feeding study in male rats, one feeding study in female rats, and two feeding studies in male and female rats. Aroclor 1260 caused significant increases in the incidences of "liver tumours" in males in one study, and of hepatocellular adenoma and carcinoma in females in a second study. In a third study, Aroclor 1260 increased the incidence of hepatocellular carcinoma in females, and of cholangioma in males and females. In a fourth study, Aroclor 1260 increased the incidence of hepatocellular adenoma in males, of hepatocellular adenoma, hepatocellular carcinoma, and cholangioma in

females, and of thyroid follicular cell adenoma in males.

5.3.3 Clophen

In one feeding study of carcinogenicity in male rats, Clophen A 30 caused a significant increase in the incidence of benign hepatocellular tumours.

In one feeding study of carcinogenicity in male rats, Clophen A 60 caused significant increases in the incidence of benign hepatocellular tumours and hepatocellular carcinoma.

5.3.4 Kanechlor

Kanechlor 300 gave negative results when tested for carcinogenicity in one feeding study in male and female mice, and one feeding study in male mice.

Kanechlor 400 was tested for carcinogenicity in one feeding study in male and female mice, one feeding study in male mice, and one feeding study in male and female rats. Kanechlor 400 was also tested in three initiation–promotion studies examining promoting activity, one in rats and two in mice. Both studies of carcinogenicity in mice gave negative results. The results of the study of carcinogenicity in rats were inconclusive. Kanechlor 400 promoted hepatocellular tumours in one initiation–promotion study in rats, and in one initiation–promotion study in mice.

Kanechlor 500 was tested for carcinogenicity in one feeding study in male mice, one feeding study in male and female mice, and one initiation–promotion study of transplacental/perinatal exposure in male and female rats. It was also tested in three initiation–promotion studies, one in rats and two in mice, examining promoting activity. Kanechlor 500 caused significant increases in the incidence of hepatocellular carcinoma in both studies of carcinogenicity in male and female mice. Transplacental/perinatal administration of Kanechlor 500 decreased the incidence of NDEA-initiated tumours of the liver in rats. Kanechlor 500 promoted hepatocellular tumours in the three initiation–promotion studies.

5.4 Mechanistic and other relevant data

5.4.1 Absorption, distribution, metabolism, and elimination

(a) Absorption

In humans, gastrointestinal absorption of PCBs was estimated to vary from 50% of the ingested amount to close to 100%, the absorption decreasing as the number of chlorine atoms of the congener increased. A similar situation was observed in experimental animals. Although no quantitative data were available regarding absorption of PCBs in humans exposed by inhalation, the levels of residues detected in individuals exposed to high concentrations of PCBs in air suggested that inhaled PCBs are absorbed to a substantial extent. Data from experimental animals indicated that inhalation of PCBs gives a higher uptake of PCBs than ingestion. Studies assessing dermal exposure to commercial PCB mixtures in humans and animals showed that this route of exposure generally results in absorption levels of between 20% and 40%, with dermal penetration varying inversely with the degree of chlorination of the mixture administered. First-pass metabolism at the site of dermal exposure appears to be responsible for differences in metabolism and disposition between routes of administration. The rate of absorption and the disposition of PCBs after dermal administration may be mediated by transdermal metabolism.

(b) Distribution

PCBs are lipophilic compounds that are preferentially retained and may accumulate in adipose tissue and lipid-rich tissues. A few studies mentioned substantial retention of certain congeners in the lung and spleen in mice and rats, respectively. The pattern of congeners observed in tissues of humans or experimental animals does not correspond to the congener profiles of PCB formulations. The major PCB components in the plasma and adipose tissue of occupationally exposed individuals are the hexa- and heptachlorobiphenyls. PCB congeners with chlorine atoms in the *para* positions are generally found at relatively high concentrations, while PCBs with unsubstituted *meta*,*para* positions on at least one ring are present at lower concentrations. The most abundant congeners found in adipose tissue, plasma, and liver are 2,2′,3,4,4′,5′-hexachlorobiphenyl (PCB-138), 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB-153) and 2,2′,3,4,4′,5,5′-heptachlorobiphenyl (PCB-180). PCBs have been found to cross the blood–brain barrier, and data from humans and experimental animals provided clear evidence for the transplacental passage of these chemicals. Metabolites of PCBs, including hydroxylated PCBs and methylsulfone PCBs, are also known to distribute to various tissues.

(c) Metabolism

Individual PCB congeners differ greatly in the ease with which they are metabolized in humans and animals. Congeners with four or fewer chlorines and those with adjacent unsubstituted *meta*,*para* positions are metabolized more readily than those with more than four chlorines and with substituents at *meta*,*para* ring positions. The initial step in the biotransformation of all PCB congeners is cytochrome P450 (CYP)-dependent mono-oxygenation. Readily metabolized congeners can be converted to potentially electrophilic and genotoxic metabolites of PCBs, arene oxides, and quinones. Quinones arise from dihydroxylated PCB metabolites through the action of peroxidases or prostaglandin endoperoxide synthase. The other major pathway of metabolism of PCBs is conversion of an arene oxide metabolite to a glutathione conjugate. The glutathione conjugate is then converted either to the excreted non-toxic mercapturic acid, or to the generally poorly excreted methyl sulfone metabolite.

(d) Elimination

Highly chlorinated congeners persist in the body, with half-lives averaging about 8–15 years; the half-lives of less chlorinated PCBs are distinctly shorter. In addition, PCB half-lives vary according to species, being longer in humans than in experimental animals, including monkeys. PCBs are mainly excreted via the faeces, while urine usually represents a minor route of excretion. Faecal excretion concerns not only unabsorbed PCBs, but also the excretion of biliary metabolites in the intestine. The proportion as well as the rate of elimination in the excreta depends on the type of mixture or congener and the route of exposure. Excretion profiles, and metabolite profiles in excreta, were different after administration of a dermal dose of PCBs when compared with an equivalent intravenous dose.

In addition to hydroxylated and dihydroxylated PCBs, the corresponding glucuronide and sulfate conjugates, as well as mercapturic acids, have also been characterized in the urine. Lactation is also a major route of excretion of PCBs in animals and humans. Minor routes of excretion such as elimination through the intestinal wall in the gastrointestinal tract or via the skin may also occur.

5.4.2 Genetic and related effects

A very limited number of studies in humans was available on cytogenetic effects in peripheral lymphocytes (chromosomal aberration, sister-chromatid exchange, micronucleus formation) and urinary concentrations of 8-hydroxy-2′-deoxyguanosine (8-OHdG) in populations with possible exposure to PCBs. Although all these studies provided valuable information on genetic and related effects in humans exposed occupationally and environmentally to PCBs, the interpretation and generalization of the results was hindered by lack of information about PCB exposure, analysis, and levels, the lack of a real unexposed control population, the small number of individuals examined, confounding exposure to other chemicals, and lifestyle factors.

Several reports of sperm DNA damage and chromosome aneuploidy indicated that the testis may be a target organ for toxicity associated with PCBs.

Some very recent studies indicated that PCBs affect DNA methylation patterns in exposed humans, with long-term consequences for gene expression and chromosome stability. Since genes encoding for steroid hormone-synthesizing enzymes and oncogenes have been shown to be targeted, this may have significant implications for a possible mode of action of carcinogenesis by PCBs.

There was a lack of data about levels or even occurrence of individual PCB congeners in publications on the genotoxic effects of PCBs in humans. Only a few recent studies had analysed a very small number of congeners and calculated correlations with biological effects. Statistically positive correlations were found between serum concentration of PCB-118 and formation of micronuclei and DNA strand breaks (comet assay) in peripheral lymphocytes, serum concentrations of PCB-153 and DNA fragmentation in sperm, serum concentrations of PCB-138 and PCB-153 and *KRAS* mutation in tumours of the pancreas and brain, and PCB-95 concentrations and autism with a genetic basis (maternal dup15q11–q13 and Prader-Willi syndrome). These were interesting observations, but not sufficient to allow a structure–activity correlation.

Of all the commercial PCB mixtures, Aroclor 1254 has been by far the most extensively investigated for genetic effects in vitro and in vivo. Although numerous studies in vitro and in vivo with a negative outcome have been reported, almost none are suitable for hazard assessment, primarily due to the low doses tested and, in case of studies in vitro, the lack of an exogenous metabolic system. Thus the Working Group concluded, on the basis of a positive test for cell transformation and a weakly positive study of mutagenicity in transgenic mice in vivo, that mutagenicity associated with long-term exposure to Aroclor 1254 cannot be excluded with certainty.

Studies of mutagenicity with individual PCBs were available for 13 congeners. The most frequently investigated congener was monochlorinated PCB-3 and its metabolites, and studies in vitro and in vivo provided clear evidence that PCB-3 causes mutation in vitro and in vivo. However, metabolic activation to electrophilic species, i.e. quinones, is required, as shown by direct testing of PCB-3 metabolites for gene mutagenicity in vitro. The experimental evidence overall suggested that both DNA-adduct formation and generation of reactive oxygen species must be considered equally plausible modes of action.

Since both in-vitro and in-vivo studies provided evidence that PCB congeners with up to four chlorines are metabolically activated to electrophilic species that cause an increase in DNA-adduct levels, it seems likely that PCBs with one to four chlorines have the same mode of action as PCB-3. In contrast, strong evidence suggested that decachlorinated PCB-209 is very unlikely to cause mutations.

For dioxin-like PCB-126, a dose-dependent increase in DNA-adduct formation – resulting from lipid peroxidation or oxidative damage of the DNA backbone – has been reported in rats exposed to PCB-126 in the long-term. Thus, a genotoxic mechanism, probably via generation of reactive oxygen species, seems to contribute to the mode of action of PCB-126.

For non-dioxin-like PCB-153, a complete lack of genotoxic activity cannot be established with certainty since three in-vitro studies gave positive results. However, mechanistic follow-up studies in vitro and/or in vivo were not available to the Working Group. Thus, the relevance of this finding remains elusive.

For all other nine PCB congeners tested, i.e. PCB-15, PCB-47, PCB-52, PCB-77, PCB-101, PCB-118, PCB-138, PCB-155, and PCB-180, the Working Group considered that the results did not allow a clear conclusion to be drawn.

5.4.3 Cellular and biochemical effects

PCB congeners can be categorized according to their degree of chlorination, substitution pattern, and binding affinity to receptors. Individual PCB congeners activate receptors, including the aryl hydrocarbon, constitutive androstane, and pregnane xenobiotic receptors, and modulate gene expression controlled by these receptors/transcription factors.

(a) Cell death and proliferation

Twelve PCB congeners that have a strong affinity for the aryl hydrocarbon receptor are referred to as "dioxin-like PCBs." Activation of the aryl hydrocarbon receptor is one of the key events linked to carcinogenesis mediated by dioxin-like compounds. Besides its role in induction of CYP1 enzymes (linked to toxicity and cancer initiation), sustained activation leads to deregulation of cell-cycle control and cell proliferation, inhibition of apoptosis, suppression of cell–cell communication and adhesion, and increased cell plasticity and invasiveness. In accordance with the concept of toxic equivalency, PCB-126 is the most potent aryl-hydrocarbon receptor agonist of the PCBs, followed by PCB-169; mono-*ortho* chlorinated PCBs (e.g. PCB-118, PCB-156), and PCB-77 also activate the aryl hydrocarbon receptor, although to a lesser extent.

On the other hand, non-dioxin-like PCBs induce many of their effects via multiple aryl hydrocarbon receptor-independent mechanisms, including activation of the constitutive androstane or pregnane X receptors, and perturbations in cell–cell communication and cell adhesion. Non-dioxin-like PCBs induce production of reactive oxygen species, activation of NF-κB transcription factors, and suppression of plasma membrane proteins, constituents of gap, adherens, and tight junctions, all of which may play a significant role in tumour promotion and progression. A series of non-dioxin-like PCBs, including less chlorinated congeners (e.g. PCB-18, PCB-47, PCB-52, and PCB-74), environmentally abundant congeners (e.g. PCB-138 and PCB-153), and hydroxylated metabolites, such as 3′,4′-di(OH)PCB-5, 4-OH-PCB-109 (4-OH-2,3,3′,4′,5-pentaCB), and 4-OH-PCB-187, inhibited gap junction intercellular communication in rat liver epithelial cells. A mixture of seven non-dioxin-like PCBs (PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, PCB-180, and PCB-209) induced production of reactive oxygen species and cell motility in human breast cancer cells. Both the dioxin-like congener PCB-126, and the non-dioxin-like congeners PCB-118 and PCB-153 disrupted the expression of cytosolic scaffold proteins of tight junctions in brain endothelial cells in mice. Expression of anti-apoptotic *Bcl2* gene in a short-term study in female rat liver, to decrease apoptotic index and to suppress the levels of gap junction and adherens junction proteins (connexin 43, β-catenin, E-cadherin) in rat liver epithelial cells. PCB-28, PCB-101, PCB-153, and also PCB-187 (to a lesser

extent) suppressed apoptosis in rat hepatocytes and human hepatoma HepG2 cells.

(b) Endocrine disruption

Population-based studies in men and women have shown an inverse correlation between serum concentrations of PCBs and circulating testosterone, including testosterone bound to sex-hormone-binding globulin. Studies on mother–infant pairs showed an inverse relationship between indicator PCBs and testosterone in female infants, which was statistically significant with the mono-*ortho* congeners PCB-105 and PCB-118, while male infants showed a stronger reduction in estradiol with higher serum concentrations of PCBs.

In studies on extracts of PCBs from human serum, higher serum PCB concentrations correlated with lower activities of the estrogen, androgen, and aryl hydrocarbon receptors.

The observed inverse trend between dioxin-like PCBs and activities of the aryl hydrocarbon and estrogen receptors suggests that these compounds have anti-estrogenic activity. In cultured cells, highly chlorinated congeners generally act as anti-estrogens and their hydroxylated metabolites are more active than the parent compound. In contrast, less chlorinated PCBs and their hydroxylated metabolites are generally estrogenic, and their potency is dependent upon *ortho* chlorination and *para* hydroxylation; estrogenic activities of the hydroxylated metabolites of less chlorinated PCBs were reported to be additive.

Studies with cultured cells demonstrated that some PCBs are androgen-receptor antagonists, the anti-androgenic effects of dioxin-like PCBs being more pronounced than those of *ortho*-substituted PCBs. This antagonism has been associated in humans with several factors related to an increased risk of cancer of the testis.

In population-based studies, an inverse correlation was also reported between total serum PCBs and triiodothyronine, thyroxine, and thyroid-stimulating hormone. For hydroxylated PCBs, a positive correlation was found with free thyroxin in umbilical cord tissue of fetuses after in-utero exposure.

Studies in rats demonstrated that hydroxylated PCBs that bind to the thyroid receptor act as agonists to the thyroid hormone; one metabolite even displayed a higher binding affinity than does thyroxine, the natural ligand. PCBs with chlorines in the *ortho* position only have significant binding affinity for the transport protein transthyretin.

Hydroxylated PCBs may cross the placental barrier, probably through binding to transthyretin, thus causing a reduction of total and free thyroxine concentrations in fetal plasma and brain. Moreover, pre- and postnatal exposure to PCBs and their hydroxylated metabolites can interfere with the thyroid-hormone system, which may lead to a decrease in levels of thyroid hormone.

Disturbance of thyroxine-binding to transthyretin by PCB metabolites and increased glucuronidation causes a reduction in serum thyroxine concentrations in Aroclor 1254-exposed rats. The interference of PCBs with the thyroid system in vitro as well as in animals corroborates the effects observed in human population studies. The effects of PCBs on thyroid-hormone function, metabolism and transport may increase the risk for toxicity and pre-cancerous processes.

In a study that considered 10 different mechanisms to establish in-vitro toxicity profiles for 24 PCB congeners, hierarchical cluster analysis showed that 7 indicator PCBs contributed most to the anti-androgenic, (anti)estrogenic, and anti-thyroidal effects of PCBs reported to be present in human samples.

(c) Effects on the immune system

The limited data available for human exposure suggested that PCBs may cause immunosuppression. PCBs can affect an impressive number of immune parameters that include

changes in bone-marrow cellularity; shifts in T-lymphocyte subsets and function; thymus and spleen atrophy, which correlate strongly with humoral and cell-mediated immunosuppression; reduced resistance to microbial infection; and a compromised immune-surveillance mechanism. Alterations in the immune system and immunotoxicity were also reported after PCB exposure during prenatal or early life.

An estimation of the degree of immunotoxicity induced by various PCB congeners and mixtures is hindered by the fact that several species with significant differences in sensitivity were used across the studies, with different routes of exposure and levels of treatment. In general, doses of > 1 mg/kg bw per day of the highly chlorinated commercial PCB mixtures (Aroclors 1248, 1254, 1262, and 1260) were more immunotoxic than the less chlorinated PCB mixtures. The few individual congeners tested in rats caused only minor changes in the thymus without affecting other parameters of the immune system.

Non-human primates are more sensitive to PCB-induced immunotoxicity. In long-term studies in rhesus monkeys exposed at levels similar to those in humans, a consistent finding was the significantly suppressed response to challenge with sheep red blood cell antigen in adult and infant monkeys. Similar results were observed in many other experimental animals at higher concentrations of PCBs.

The humoral immune response to sheep red blood cell antigen is the most predictive of the tests currently used in immunotoxicology, and has been used in the calculation of TEFs. The TEF calculation is based on the assumptions that the effects of PCBs on the immune system are mediated through the aryl hydrocarbon receptor, and that PCBs in mixtures may have an additive effect. Nonetheless, certain PCBs exert their immunotoxic effects by mechanisms that are not mediated through the aryl hydrocarbon receptor; such effects are thought to be mediated via metabolism to arene-oxide intermediates capable of alkylating critical cellular macromolecules. Additionally, certain non-dioxin-like PCBs may antagonize the immunotoxic effects of other chemicals, including those of dioxin.

The effects on the immune system were shown to persist in children at a later age. The severity of effects correlated with PCB concentrations in the children's blood, or with those in maternal blood during pregnancy and lactation. Similar results were obtained in experimental animals.

(d) Effects on the inflammatory response

Exposure to PCBs has been associated with the development of inflammation in several studies in experimental animals in vivo; chronic active inflammation can be detected specifically in tissues that are affected by PCB exposure.

In in-vivo studies in mice, it has been reported that PCB-77, PCB-104, and PCB-153 are associated with inflammation in target organs since they induced the production of specific inflammatory mediators, including intercellular adhesion molecules (e.g. ICAM, VCAM-1, MCP-1) in the liver, lungs, and brain. The tissue distribution of these inflammatory mediators varied according to the congener administered, probably due to differences in congener accumulation in the various organs.

PCBs have also been shown to cause vascular inflammation in vivo.

In vitro, PCB-153 may induce expression of several pro-inflammatory cytokines through NF-κB pathway inhibitor.

Several PCB congeners and mixtures, including Aroclor 1242 and PCB-47, interfere with O_2^- elimination by suppressing the activity of superoxide dismutase which converts O_2^- to H_2O_2. Non-dioxin-like PCBs are capable of stimulating neutrophil O_2^- production, while dioxin-like congeners with a high affinity for the aryl hydrocarbon receptor do not activate neutrophils to produce O_2^- and may inhibit this response.

Certain congeners (PCB-77, PCB-114, PCB-126, and PCB-169) disrupted the normal functions of the vascular endothelium, thus allowing increased transfer of albumin across endothelial monolayers. The same congeners enhanced oxidative stress, increased production of interleukin-6 by endothelial cells, increased the levels of intracellular calcium, increased the activity of cytochrome P450 1A, enhanced expression of the adhesion molecule VCAM-1, and decreased levels of vitamin E in the culture medium. In contrast, PCB-153 did not have an effect on cellular oxidation or on endothelial barrier function.

5.4.4 Classification of congeners and quantitative structure–activity relationships

Different key structural determinants of the toxicity of individual PCB congeners were identified in various in-vitro assays for specific effects of tumour promotion, endocrine disruption, and neurotoxicity. Multivariate toxicity profiling of a series of PCB congeners indicated that many of the responses are due to different structure–activity relationships and cannot be integrated. The use of quantitative structure–activity relationships is also hampered at present by the lack of data on specific cancer-related modes of action for larger sets of congeners.

5.4.5 Hepatic preneoplastic lesions

Numerous studies have used preneoplastic lesions as end-points to study the effects of PCBs on two-stage hepatocarcinogenesis. PCBs have promoting activity, especially congeners and mixtures that activate the aryl hydrocarbon and/or constitutive androstane receptors. When non-*ortho* and di-*ortho* PCBs are coadministered, less than additive effects are observed in most studies, while administration of two non-*ortho* PCBs is additive. Several less chlorinated PCBs have initiating activity.

5.4.6 Organ toxicity

Organ toxicity relevant to the carcinogenicity of long-term exposure to PCB congeners and commercial mixtures of PCBs in experimental systems is observed in the liver and also in other organs, notably the lung and thyroid.

5.4.7 Effects on skin

Chloracne and other dermal alterations are well-known effects that have been reported in workers exposed occupationally to PCBs, and in individuals exposed by accidental ingestion of rice oil contaminated with high concentrations of PCBs (Yusho and Yucheng victims). Chloracne generally appears in individuals with serum PCB concentrations that are 10–20 times higher than those of the general population, but there is large variability between individuals. At birth, children exposed in utero during food poisoning incidents had increased rates of hyperpigmentation, eyelid swelling and discharge, deformed nails, and acne, compared with controls.

Long-term oral administration of relatively low doses of PCBs to rhesus monkeys resulted in dermal alterations similar to those observed in humans exposed at high concentrations. Offspring from monkeys exposed during gestation and nursed by exposed mothers also developed dermal alterations after a few weeks of suckling. Rodents also develop skin alterations, but only after high exposures to PCBs.

Exposure of normal human melanocytes to TCDD resulted in activation of the aryl hydrocarbon receptor signalling pathway, an aryl hydrocarbon receptor-dependent induction of tyrosinase and – as a consequence – an elevated total melanin content. These effects were due to the induction of expression of tyrosinase and tyrosinase-related protein 2 genes. Thus, the

aryl hydrocarbon receptor is able to modulate melanogenesis by controlling the expression of melanogenic genes. This lends biological plausibility to the epidemiological findings of increased risks of melanoma of the skin after exposure to PCBs.

5.4.8 Susceptible populations

(a) Genetic polymorphisms

Differences in response to individual congeners may arise from polymorphisms in the genes for CYP, the aryl hydrocarbon receptor and repressor, and other enzymes and receptors that interact with endogenous molecules such as steroid hormone receptors. Studies in the most highly exposed populations reported a higher incidence of cancer of the breast in women with the *CYP1A1*2C* genotype; of non-Hodgkin lymphoma and a polymorphism in the gene encoding the aryl hydrocarbon receptor; and of skin lesions in Yucheng victims who had the *CYP1A1*2C* polymorphism and were null for *GSTM1*.

(b) In-utero and postnatal exposure

PCBs can pass through the placenta during embryonic development and is excreted in breast milk. In addition, compared with adults, children have a lower barrier to absorption through the skin, gastrointestinal tract, and lungs, and lower levels of detoxifying enzymes. A combination of all these factors leads to a higher accumulation of PCBs in children. The determination of PCB concentrations in cord blood, breast milk, and in tissues of mother/infant have contributed significantly to the understanding of the movement of these compounds from mother to infant and their distribution patterns throughout the body.

A significant dose-dependent relationship exists between the duration of breastfeeding and the concentration of the sum of congeners PCB-101, PCB-118, PCB-138, PCB-153, PCB-170, PCB-180, PCB-183, and PCB-187. Exclusive breastfeeding beyond 12 weeks was associated with a doubling in the whole blood concentration of PCBs compared with bottle-fed children.

Elimination kinetic studies in children with elevated PCB concentrations as a result of breastfeeding revealed differences in congener half-lives. The longest half-lives corresponded to elimination of the parent PCB only, with a daily fat excretion rate of 1–2 g, while shorter half-lives were attributable to metabolic breakdown.

Long-term studies in non-human primates receiving Aroclor 1254 have shown that in tissues of mother/infants with higher concentrations of PCBs, a dramatic shift from tetra- and hexachlorobiphenyls to penta-and heptachlorobiphenyls was observed. The PCB distribution pattern in tissues from a dosed mother/infant pair differed between mother and infant, with a larger percentage of heptachlorobiphenyls in the infant than in its dam. PCB concentrations in the infant's blood declined rapidly and approached maternal levels within 40–50 weeks; at 100 weeks after weaning, PCB concentrations in the adipose tissue of exposed infants were similar to background levels found in the control group.

Tissue retention/accumulation of PCBs in postnatal and prepubertal studies in mice showed results consistent with the well known effect of chlorine-substitution pattern on the rate of metabolism. In the lung, all congeners except PCB-153 were retained and decreased in amount only as a function of dilution due to growth. The selective retention of congeners with high affinity for the aryl hydrogen receptor is of interest since it is a property that correlates with toxicity and tumour promotion. In the liver, retention of all congeners was observed during the prepubertal growth phase, with specific enrichment of PCB-105, followed subsequently by more rapid depletion of certain congeners.

Prenatal/postnatal (through breastfeeding) exposure to PCBs can affect the dynamics of cell-surface receptor expression on lymphoid cells. These effects result in dysfunctional

immune responses, which may have adverse immune-system related consequences on the health of infants and toddlers. Furthermore, PCB-induced effects on the thymus and natural killer cells have been reported in children, and these effects may play a role in the development of leukaemia in these children.

5.4.9 Mechanistic considerations

PCBs and their metabolites have multiple modes of action. Less chlorinated congeners involved in oxidative metabolism may produce oxidative stress and genotoxicity; highly chlorinated congeners are very persistent and interact with various receptors including the aryl hydrocarbon, constitutive androstane, pregnane-X (controlling xenobiotic and steroid hormone metabolism and other processes), and steroid nuclear receptors such as the androgen and estrogen receptors. Additionally, PCBs modulate plasma membrane-associated proteins affecting cell communication, adhesion and migration, and also act as tumour promoters. Overall, PCBs occur and act in complex mixtures eliciting both genotoxic and nongenotoxic effects associated with carcinogenesis, tumour promotion, and progression.

6. EVALUATION AND RATIONALE

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of polychlorinated biphenyls (PCBs). PCBs cause malignant melanoma. Positive associations have been observed for non-Hodgkin lymphoma and cancer of the breast.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of PCBs.

There is *sufficient evidence* in experimental animals for the carcinogenicity of PCB-126, PCB-118, Aroclor 1260, Aroclor 1254, and Kanechlor 500.

There is *limited evidence* in experimental animals for the carcinogenicity of PCB-153, 4′-OH-PCB-30, 4′OH-PCB-61, Aroclor 1242, Aroclor 1016, Clophen A30, and Clophen A60.

There is *inadequate evidence* in experimental animals for the carcinogenicity of PCB-138, Kanechlor 300, and Kanechlor 400.

Congeners for which there is *sufficient evidence* in experimental animals for carcinogenicity (PCB-126 and PCB-118) are agonists of the aryl hydrocarbon receptor and exhibit dioxin-like properties. Commercial mixtures for which there is *sufficient evidence* in experimental animals for carcinogenicity are highly chlorinated and are known to include aryl-hydrocarbon receptor agonists that exhibit dioxin-like properties, as well as agonists of the constitutive androstane receptor.

The commercial mixtures for which there is *limited evidence* in experimental animals generally have a low degree of chlorination, but are also known to contain congeners that are agonists of the aryl hydrocarbon and/or constitutive androstane receptors. The relative contributions of the different congeners (dioxin-like and non-dioxin-like) to the carcinogenicity of the commercial mixtures is not known.

6.3 Overall evaluation

PCBs are *carcinogenic to humans (Group 1).*

"Dioxin-like" PCBs, with a toxicity equivalency factor (TEF) according to WHO (PCB-77, PCB-81, PCB-105, PCB-114, PCB-118, PCB-123, PCB-126, PCB-169, PCB-156, PCB-157, PCB-167, PCB-189), are *carcinogenic to humans (Group 1).*

6.4 Rationale

In making this overall evaluation, the Working Group considered that:

- There is strong evidence to support a receptor-mediated mechanism for carcinogenesis associated with dioxin-like PCBs in humans, based upon demonstration of carcinogenicity in experimental animals and upon extensive proof of activity identical to 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) for every step of the mechanism described for

TCDD-associated carcinogenesis in humans, including receptor binding, gene expression, protein-activity changes, cellular replication, oxidative stress, promotion in initiation–promotion studies and complete carcinogenesis in experimental animals.

- However, the carcinogenicity of PCBs cannot be attributed solely to the carcinogenicity of the dioxin-like PCBs.